

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 96,877-W1)

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| In the Application of: |) | |
| |) | |
| Lum et al. |) | Examiner: M. Berch |
| |) | |
| Serial No. Unknown |) | Group Art Unit: 1624 |
| |) | |
| Filed: August 14, 2001 |) | |
| |) | |
| Title: Purine Inhibitors of |) | |
| Cyclin Dependent Kinase 2 |) | |
| and IκB-α |) | |

PRELIMINARY AMENDMENT TO ACCOMPANY
CONTINUING APPLICATION

Assistant Commissioner for Patents
Patent and Trademark Office
Washington, D.C. 20231

Dear Sir:

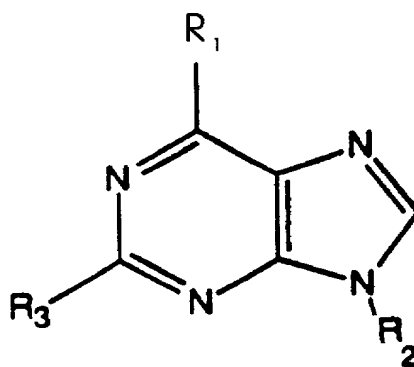
Please amend the application claims as follows before calculating the application
filing fee:

IN THE CLAIMS

Cancel application claims 1-49 without prejudice.

Add the following new claims 50-90 to the application:

50. (New) A 2,6,9-trisubstituted purine composition of matter having the following
formula:



(I)

wherein R_1 is halogen or R'_1-X wherein $X = NH, O, S, S(O_2)$.

R'_1 is alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, CF_3 , heteroaryl, heterocyclyl, R^{22} , SR^{20} , $S(O)R^{21}$, SO_2R^{21} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20} , $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN , CO_2R^{20} , $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20} ;

R_2 is a hydrogen or hydrocarbon selected from the group alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22} , SR^{20} , $S(O)R^{21}$, SO_2R^{21} , $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20} ,

$\text{OCONR}^{20}\text{R}^{23}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{R}^{23}$, CN , CO_2R^{20} , $\text{CONR}^{20}\text{R}^{23}$,
 $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$ and COR^{20} ;

R_3 is $-\text{NR}_4\text{R}_5$, wherein R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22} , SR^{20} , $\text{S}(\text{O})\text{R}^{21}$, SO_2R^{21} , $\text{SO}_2\text{NR}^{20}\text{R}^{23}$, $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{NR}^{20}\text{R}^{23}$, $\text{NR}^{20}\text{COR}^{21}$, $\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$, $\text{N}(\text{R}^{20})\text{C}(\text{NR}^{20})\text{NHR}^{23}$, $\text{NR}^{20}\text{SO}_2\text{R}^{21}$, OR^{20} , $\text{OCONR}^{20}\text{R}^{23}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{R}^{23}$, CN , CO_2R^{20} , $\text{CONR}^{20}\text{R}^{23}$, $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$ and COR^{20} , with the proviso that either R_4 or R_5 must be substituted with $\text{NR}_{20}\text{R}_{23}$, and wherein when R_3 is 2-hydroxyethylamino and R_2 is methyl then $\text{R}_1'\text{-X}$ is not amino, 3-methyl-2-butenylamino, benzylamino, or m-hydroxybenzylamino, and wherein when R_3 is not 2-hydroxyethylamino and R_2 is isopropyl, then $\text{R}_1'\text{-X}$ is not benzylamino, m-hydroxybenzylamino, or 3-methylbutylamino, and wherein when R_3 is 2-hydroxyethylamino and R_2 is 2-hydroxyethyl, then $\text{R}_1'\text{-X}$ is not benzylamino and wherein when R_3 is selected from the group consisting of 2-methyl-2-hydroxypropylamino and 2-dimethylaminoethylamino, and when R_2 is methyl, then $\text{R}_1'\text{-X}$ is not benzylamino;

R^{20} is a member selected from the group consisting of H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents

independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C₁₋₆ alkyl, CF₃, aryl, and heteroaryl;

R²¹ is a member selected from the group consisting of C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group of halo, heterocyclyl, aryl, heteroaryl, CF₃, CN, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CO₂R²², SO₂NR²⁰CON(R²⁰)₂, N(R²⁰)₂ NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OR²⁰, OCONR²⁰SO₂R²², OC(O)R²⁰, C(O)OCH₂OC(O)R²⁰, and OCON(R²⁰)₂, and each optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, alkyl, CF₃, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, NCOR²², NR²⁰SO₂R²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, NR²⁰CON(R²⁰)₂, OC(O)R²⁰, OC(O)N(R²⁰)₂, SR²⁰, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, or OR²⁰;

R²² is a member selected from the group consisting of C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C₁₋₆ alkyl, CF₃, aryl, and heteroaryl; and

R²³ is R²¹ or H.

51. (New) A 2,6,9-trisubstituted purine composition of claim 50 wherein:

R'₁ is a alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, CF₃, aryl, heteroaryl, heterocyclyl, R²², SR²⁰, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, OR²⁰, CN, CO₂R²⁰, CONR²⁰R²³, and COR²⁰;

R₂ is a hydrogen or hydrocarbon selected from the group substituted alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R²², SR²⁰, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, OR²⁰, CN, CO₂R²⁰, CONR²⁰R²³, and COR²⁰;

R₄ and R₅ are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R²², SR²⁰, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, OR²⁰, CN, CO₂R²⁰,

CONR²⁰R²³, and COR²⁰ with the proviso that either R₄ or R₅ must be substituted with NR₂₀R₂₃;

R²⁰ is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈ alkenyl, C₂₋₁₅ heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C₁₋₆ alkyl, CF₃, aryl, and heteroaryl;

R²¹ is a member selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group of halo, heterocyclyl, aryl, heteroaryl, CF₃, CN, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CO₂R²², SO₂NR²⁰CON(R²⁰)₂, N(R²⁰)₂NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OR²⁰, OCONR²⁰SO₂R²², OC(O)R²⁰, C(O)OCH₂OC(O)R²⁰, and OCON(R²⁰)₂, and each optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, alkyl, CF₃, amino, mono- or di-alkylamino, alkyl or aryl or heteroaryl amide, NCOR²², NR²⁰SO₂R²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, NR²⁰CON(R²⁰)₂, OC(O)R²⁰, OC(O)N(R²⁰)₂, SR²⁰, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, or OR²⁰; and

R²² is a member selected from the group consisting of C₁₋₈ alkyl, C₂₋₈alkenyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl,

mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C₁₋₆ alkyl, CF₃, aryl, and heteroaryl.

52. (New) A 2,6,9-trisubstituted purine composition of claim 50 wherein:

R'₁ is alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, CF₃, aryl, heteroaryl, heterocyclyl, R²², SR²⁰, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰SO₂R²¹, OR²⁰, CN, CO₂R²⁰, CONR²⁰R²³, and COR²⁰;

R₂ is a hydrogen or hydrocarbon selected from the group including alkyl, heterocyclyl, and aryl, each having one to 10 carbon atoms, which alkyl, heterocyclyl, aryl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R²², SR²⁰, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰SO₂R²¹, OR²⁰, CN, CO₂R²⁰, CONR²⁰R²³, and COR²⁰;

R₄ and R₅ are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R²², SR²⁰, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰SO₂R²¹, OR²⁰, CN, CO₂R²⁰, CONR²⁰R²³, and COR²⁰ with the proviso that either R₄ or R₅ must be substituted with NR₂₀R₂₃;

R^{20} is a member selected from the group consisting of H, C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, $O-C_{1-6}$ alkyl, CF_3 ;

R^{21} is a member selected from the group consisting of C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3 , CN, OR^{20} , SR^{20} , $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $NR^{20}SO_2R^{22}$, OR^{20} ; and

R^{22} is a member selected from the group consisting of C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, $O-C_{1-6}$ alkyl, CF_3 , aryl, and heteroaryl.

53. (New) A 2,6,9-trisubstituted purine composition of claim 50 wherein:

R'_1 is a alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3 , aryl, R^{22} , SR^{20} , $S(O)R^{21}$, SO_2R^{21} , $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20} , CN, CO_2R^{20} , and $CONR^{20}R^{23}$;

R_2 is a hydrogen or hydrocarbon selected from the group alkyl, heterocyclyl, and aryl, each having one to 10 carbon atoms, which alkyl, heterocyclyl, aryl, are optionally substituted with from 1 to 2 substituents independently selected from the group consisting

of halo, aryl, heteroaryl, heterocyclyl, R^{22} , SR^{20} , $S(O)R^{21}$, SO_2R^{21} , $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20} , CN, CO_2R^{20} , $CONR^{20}R^{23}$, and COR^{20} ;

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, R^{22} , SR^{20} , $S(O)R^{21}$, SO_2R^{21} , $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20} , CN, CO_2R^{20} , and $CONR^{20}R^{23}$ with the proviso that either R_4 or R_5 must be substituted with $NR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O- C_{1-6} alkyl, CF_3 ;

R^{21} is a member selected from the group consisting of C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3 , CN, OR^{20} , SR^{20} , $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $NR^{20}SO_2R^{22}$, OR^{20} ; and

R^{22} is a member selected from the group consisting of C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O- C_{1-6} alkyl, CF_3 , aryl, and heteroaryl.

54. (New) The 2,6,9-trisubstituted purine composition of claim 50 wherein $X=NH$.

55. (New) The 2,6,9-trisubstituted purine composition of claim 52 wherein R_1' is selected from the group consisting of aralkyl and heteroarylalkyl.

56. (New) The 2,6,9-trisubstituted purine composition of claim 55 wherein R_1' is selected from the group consisting of aralkyl, unsubstituted pyridylalkyl and substituted pyridylalkyl and wherein R_2 is selected from the group consisting of lower alkyl, substituted lower alkyl, and alkyl cycloalkyl.

57. (New) A 2,6,9-trisubstituted purine composition of claim 54 wherein:

R_1' is an aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, each having one to 20 carbon atoms, which aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3 , aryl, R^{22} , SR^{20} , $S(O)R^{21}$, SO_2R^{21} , $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20} , CN, CO_2R^{20} , and $CONR^{20}R^{23}$;

R_2 is a hydrogen or hydrocarbon selected from the group substituted lower alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl each having one to 10 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22} , SR^{20} , $S(O)R^{21}$, SO_2R^{21} , $NR^{20}R^{23}$, OR^{20} , and CN;

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 2 substituents

independently selected from the group consisting of halo, aryl, R^{22} , SR^{20} , $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20} , CN, CO_2R^{20} , and $CONR^{20}R^{23}$ with the proviso that either R_4 or R_5 must be substituted with $NR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-8} alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or CN, $O-C_{1-6}$ alkyl, CF_3 ;

R^{21} is a member selected from the group consisting of C_{1-8} alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3 , CN, OR^{20} , SR^{20} , $N(R^{20})_2$; and

R^{22} is a member selected from the group consisting of C_{1-3} alkyl, aryl, heteroaryl which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl, CN, $O-C_{1-6}$ alkyl, CF_3 .

58. (New) The 2,6,9-trisubstituted purine composition of claim 52 wherein R_1' is selected from the group consisting of aryl, heterocyclyl, heteroaryl, substituted heteroaryl, and substituted aryl.

59. (New) The 2,6,9-trisubstituted purine composition of claim 52 wherein R_1' is selected from the group consisting of aryl, unsubstituted pyridyl, substituted pyridyl, and substituted aryl, and R_2 is selected from the group consisting of alkyl, substituted alkyl.

60. (New) The 2,6,9-trisubstituted purine composition of claim 51 wherein R_4 and R_5 are each selected from the group consisting of hydrogen, alkyl, heterocyclyl, acyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkyl alkenyl, alkyl alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl,

heteroarylalkyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22} , SR^{20} , $S(O)R^{21}$, SO_2R^{21} , $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $NR^{20}SO_2R^{21}$, OR^{20} , CN, CO_2R^{20} , $CONR^{20}R^{23}$, and COR^{20} with the proviso that either R_4 or R_5 must be substituted with $NR^{20}R^{23}$.

61. (New) A 2,6,9-trisubstituted purine composition of claim 60 wherein:

R'_1 is an aryl, substituted aryl, each having 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3 , aryl, R^{22} , $NR^{20}R^{23}$, $NR^{20}COR^{21}$, OR^{20} , CN;

R_2 is a hydrogen or hydrocarbon selected from the group substituted lower alkyl, cycloalkyl, substituted cycloalkyl each having one to 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22} , $NR^{20}R^{23}$, OR^{20} ;

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, and heterocyclyl wherein each hydrocarbon has from 1 to 12 carbon atoms, which alkyl, and heterocyclyl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22} , SR^{20} , OR^{20} , $NR^{20}R^{23}$, CN, CO_2R^{20} , and $CONR^{20}R^{23}$ with the proviso that either R_4 or R_5 must be substituted with $NR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-8} alkyl;

R^{21} is a member selected from the group consisting of C_{1-3} alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3 , CN, OR^{20} , SR^{20} , $N(R^{20})_2$; and

R²² is a member selected from the group consisting of C₁₋₃alkyl, aryl, heteroaryl which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl, CN, O-C₁₋₆ alkyl, CF₃.

62. (New) A 2,6,9-trisubstituted purine composition of claim 60 wherein:

R'₁ is an aryl, substituted aryl, each having 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, CF₃, R²², OR²⁰, CN;

R₂ is isopropyl;

R₄ and R₅ are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, and heterocyclyl wherein each hydrocarbon has from 1 to 12 carbon atoms, which alkyl, and heterocyclyl are optionally substituted with from 1 substituent independently selected from the group consisting of R²², OR²⁰, NR²⁰R²³ with the proviso that either R₄ or R₅ must be substituted with NR₂₀R₂₃;

R²⁰ is a member selected from the group consisting of H, C₁₋₂alkyl;

R²¹ is a member selected from the group consisting of C₁₋₃ alkyl;

R²² is a member selected from the group consisting of C₁₋₃alkyl, aryl, which alkyl, aryl, are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, CN, CF₃; and

R²³ is R²¹ or H.

63. (New) A 2,6,9-trisubstituted purine composition of claim 60 wherein:

R'₁ is an aralkyl, substituted aralkyl, each having 6-8 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently

selected from the group consisting of halo, CF₃, aryl, R²², NR²⁰R²³, NR²⁰COR²¹, OR²⁰, CN;

R₂ is a hydrogen or hydrocarbon selected from the group substituted alkyl, cycloalkyl, substituted cycloalkyl each having one to 6 carbon atoms wherein substitution includes optional substitution with from 1 substituent independently selected from the group consisting of halo, R²², NR²⁰R²³, OR²⁰,

R₄ and R₅ are each independently hydrogen, or a hydrocarbon selected from the group including alkyl and heterocyclyl wherein each hydrocarbon has from 1 to 12 carbon atoms, which alkyl and heterocyclyl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R²², SR²⁰, OR²⁰, NR²⁰R²³, CN, CO₂R²⁰, and CONR²⁰R² with the proviso that either R₄ or R₅ must be substituted with NR₂₀R₂₃;

R²⁰ is a member selected from the group consisting of H, C₁₋₈alkyl;

R²¹ is a member selected from the group consisting of C₁₋₃ alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF₃, CN, OR²⁰, SR²⁰, N(R²⁰)₂; and

R²² is a member selected from the group consisting of C₁₋₃alkyl, aryl, heteroaryl which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl, CN, O-C₁₋₆ alkyl, CF₃.

64. (New) A 2,6,9-trisubstituted purine composition of claim 60 wherein:

R'₁ is -CH₂-phenyl wherein the phenyl ring is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, CF₃, R²², OR²⁰, CN;

R₂ is isopropyl;

R₄ and R₅ are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, and heterocyclyl wherein each hydrocarbon has from 1 to 12 carbon atoms, which alkyl, and heterocyclyl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of R²², OR²⁰, NR²⁰R²³ with the proviso that either R₄ or R₅ must be substituted with NR₂₀R₂₃;

R²⁰ is a member selected from the group consisting of H, C₁₋₂alkyl;

R²¹ is a member selected from the group consisting of C₁₋₃ alkyl;

R²² is a member selected from the group consisting of C₁₋₃alkyl, aryl, which alkyl, aryl, are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, CN, CF₃; and

R²³ is R²¹ or H.

65. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R₁' is selected from the group consisting of aralkyl, substituted pyridylalkyl, and unsubstituted pyridylalkyl;

R₂ is selected from the group consisting of alkyl, which alkyl is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R²², NR²⁰R²³, OR²⁰;

R₄ is a substituted alkyl having from 2 to 6 carbon atoms optionally substituted with from 1 to 3 substituents independently selected from the group consisting of R²², OR²⁰, NR²⁰R²³;

R₅ is selected from the group consisting of hydrogen, alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, R²², SR²⁰, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰SO₂R²¹, OR²⁰, CN, CO₂R²⁰, and CONR²⁰R²³ with the proviso that either R₄ or R₅ must be substituted with NR₂₀R₂₃;

R²⁰ is a member selected from the group consisting of H, C₁₋₂ alkyl;

R²¹ is a member selected from the group consisting of C₁₋₃ alkyl;

R²² is a member selected from the group consisting of C₁₋₃ alkyl, aryl, which alkyl, aryl, are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, CN, CF₃; and

R²³ is R²¹ or H.

66. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R₁' is selected from the group consisting of aryl, substituted aryl, pyridyl, and substituted pyridyl;

R₂ is selected from the group consisting of alkyl, which alkyl is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R²², NR²⁰R²³, OR²⁰;

R₄ is a substituted alkyl having from 2 to 6 carbon atoms optionally substituted with from 1 to 3 substituents independently selected from the group consisting of R²², OR²⁰, NR²⁰R²³;

R₅ is selected from the group consisting of hydrogen, alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, R²², SR²⁰, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰SO₂R²¹, OR²⁰, CN, CO₂R²⁰, and CONR²⁰R²³ with the proviso that either R₄ or R₅ must be substituted with NR₂₀R₂₃;

R²⁰ is a member selected from the group consisting of H, C₁₋₂ alkyl;

R²¹ is a member selected from the group consisting of C₁₋₃ alkyl;

R²² is a member selected from the group consisting of C₁₋₃ alkyl, aryl, which alkyl, aryl, are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, CN, CF₃; and

R²³ is R²¹ or H.

67. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R₁' is selected from the group consisting of aralkyl, pyridylalkyl, and substituted pyridylalkyl;

R₂ is selected from the group consisting of alkyl, which alkyl is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R²², and OR²⁰;

R₄ and R₅ are each alkyl having from 2 to 6 carbon atoms substituted with 1 substituent independently selected from the group consisting of R²²,

NR²⁰R²³, and OR²⁰ with the proviso that either R₄ or R₅ must be substituted with NR₂₀R₂₃;

R²⁰ is a member selected from the group consisting of H, C₁₋₂ alkyl;

R²¹ is a member selected from the group consisting of C₁₋₃ alkyl;

R²² is a member selected from the group consisting of C₁₋₃ alkyl; and

R²³ is R²¹ or H.

68. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R₁' is CH₂-Aryl or CH₂-substituted aryl, R₂ is lower alkyl, and R₄ = H, and R₅ is -CH₂CH₂NH₂, CHR'CH₂NH₂, -CH₂CHR'NH₂ wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

69. (New) The 2,6,9-trisubstituted purine composition of claim 68 wherein R₂ is isopropyl.

70. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R₁' is CH₂-Aryl or CH₂-substituted aryl, R₂ is lower alkyl, and R₄ = -CH₂CH₂OH R₅ is CH₂CH₂NH₂, or -CHR'CH₂NH₂, or -CH₂CHR'NH₂ wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

71. (New) The 2,6,9-trisubstituted purine composition of claim 70 wherein R₂ is isopropyl.

72. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R₁' is selected from the group consisting of aryl, substituted aryl, pyridyl, and substituted pyridyl, R₂ is selected from the group consisting of lower alkyl, substituted lower alkyl, and alkyl cycloalkyl, and R₄ and R₅ are each a substituted lower alkyl having from 2 to 6 carbon atoms.

73. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R_1' is benzyl substituted with a halogen, alkoxy, phenyl, pyridyl or nitro group, R_2 is isopropyl, $R_4 = H$, and $R_5 = CH_2CH_2NH_2$.

74. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R_1' is benzyl substituted with a halogen, alkoxy, C_{1-3} alkyl, CF_3 , phenyl, pyridyl or nitro group, R_2 is isopropyl, $R_4 = H$, and $R_5 = CH_2CHR'NH_2$ wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

75. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R_1' is benzyl substituted with a halogen, alkoxy, C_{1-3} alkyl, CF_3 , phenyl, pyridyl or nitro group, R_2 is isopropyl, $R_4 = H$, and $R_5 = CH_2CR'R'NH_2$ wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

76. (New) The 2,6,9-trisubstituted purine composition of claim 50 selected from the group consisting of 2-((2-hydroxyethyl)[9-(methylethyl)-6-({[4-(trifluoromethyl)phenyl]methyl}amino)purin-2-yl]amino)ethan-1-ol, (((2S)oxolan-2-yl)methyl)(6-({[4-fluorophenyl]methyl}amino)-9-(methylethyl)purin-2-yl)amine, [((2R)oxolan-2-yl)methyl)(6-({[4-fluorophenyl]methyl}amino)-9-(methylethyl)purin-2-yl)amine, (2-aminoethyl)(6-({[3,5-dichlorophenyl]methyl}amino)-9-(methylethyl)purin-2-yl)amine, (2-aminoethyl)[6-({[4-chloro-3-(trifluoromethyl)phenyl]methyl}amino)-9-(methylethyl)purin-2-yl]amine, [-(6-({[4-chlorophenyl]methyl}amino)-9-(methylethyl)purin-2-yl)amino]-3-methylbutanamide, (2-amino-2-methylpropyl)(6-({[4-chlorophenyl]methyl}amino)-9-(methylethyl)purin-2-yl)amine, 3-(2-[bis(2-hydroxyethyl)amino]-6-({[4-chlorophenyl]methyl}amino)purin-9-yl)butan-2-one,

2-[(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]-3-methylbutan-1-ol, 4-[(2-[(2-aminoethyl)amino]-9-(methylethyl)purin-6-yl)amino)methyl]benzenesulfonamide, 2-[(2-hydroxyethyl)(6-{[(4-methoxyphenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]ethan-1-ol, 2-[(2-hydroxyethyl){9-(methylethyl)-6-[(4-phenylphenyl)amino]purin-2-yl}amino]ethan-1-ol, {2-[(2-amino-2-propyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine, {2-[(2-aminoethyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine, {2-[(2-aminopropyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine and 2-[(2-aminoethyl)(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]ethan-1-ol.

77. (New) The 2,6,9-trisubstituted purine composition of claim 60 wherein R₁' is selected from the group consisting of 3-methylthiophenyl, 4-methylthiophenyl, 4-phenylbenzyl, 4-methoxybenzyl, 4-biphenyl, 3-methoxybenzyl, 4-(2-thienyl)benzyl, 4-(4-methyl)phenylbenzyl, 4-(4-trifluoromethyl)phenylbenzyl, 4-(4-nitrilo)phenylbenzyl, 4-(2-pyridinyl)benzyl, piperonyl, 3-methoxybenzyl, 4-chlorobenzyl, and 4-nitrobenzyl, and R₂ is isopropyl.

78. (New) The 2,6,9-trisubstituted purine composition of claim 77 wherein R₁' is selected from the group of compounds consisting of 4-methoxybenzyl, 4-phenylbenzyl, 4-methoxybenzyl, 4-biphenyl, 3-methoxybenzyl, 4-(2-thienyl)benzyl, 4-(4-methyl)phenylbenzyl, 4-(4-trifluoromethyl)phenylbenzyl, 4-(4-nitrilo)phenylbenzyl, 4-(2-pyridinyl)benzyl, piperonyl, 3-thiomethoxyphenyl, 4-thiomethoxyphenyl and 4-bromophenyl.

79. (New) A cationic salt of the composition of claim 50.

80. (New) An acid addition salt of the composition of claim 50.

81. A method for inhibiting cell proliferation in mammals comprising administering a therapeutically effective amount of the composition of claim 50 to the mammal.

82. (New) The method of claim 81 wherein the therapeutically effective amount ranges from about 0.001 to about 100 mg/kg weight of the mammal.

83. (New) The method of claim 81 wherein the composition is administered to a mammal suffering from a cell proliferation disorder selected from the group consisting of rheumatoid arthritis, lupus, type I diabetes, multiple sclerosis, cancer, restenosis following ballon angioplasty or atherectomy, restenosis following vascular modifying surgical procedures, host graft disease, and gout.

84. (New) The method of claim 83 wherein the cell proliferation disorder is restenosis.

85. (New) The method of claim 83 wherein the cell proliferation is disorder cancer.

86. (New) The method of claim 83 wherein the cell proliferation disorder is polycystic kidney disease.

87. (New) The method of claim 83 wherein the mammal is a human.

88. (New) A pharmaceutical composition of matter comprising the composition of claim 50 and one or more pharmaceutical excipients.

89. (New) An antifungal agent useful for treating fungal infections in humans, and animals comprising the composition of claim 50.

90. (New) The method of claim 42 wherein the cell proliferation disorder is selected from the group consisting of lymphoyd neoplasm, cancer of the colon, breast

cancer, ovarian cancer, pancreatic cancer, and cancers derived from endothelial cells.

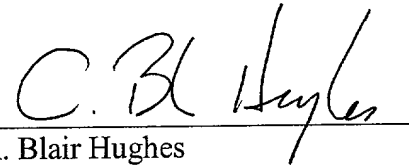
REMARKS

Claims 1-49 have been canceled without prejudice. New claims 50-90 have been added to the application. The new claims do not add new matter to the application.

Favorable consideration and early allowance of pending application claims 50-90 is courteously solicited.

Respectfully submitted,

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